MEMORANDUM

Date: October 22, 2009

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application DR1-01491

Enclosed is a letter from Dr. Xianmin Zeng of the Buck Institute for Age Research, an applicant for funding under RFA 09-01, CIRM Disease Team Research Awards. This letter was not received at CIRM five working days prior to the October ICOC meeting, but we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

I have reviewed the petition (referencing reviewer comments and the submitted application as necessary) in consultation with the CIRM scientific staff.

The applicant's petition highlights several merits and criticisms noted by reviewers. The applicant contends that reviewer criticisms were relatively minor and that the strengths of the proposal outweighed weaknesses. Upon carefully analysis of the reviewer comments, we believe that reviewers carefully considered both the overall strengths and weaknesses of this proposal and concluded that despite noted merits, there were significant concerns that appropriately placed this application in Tier 3.

The applicant indicates that they are confident their plan will achieve an IND and clinical trial in 4-5 years. However, reviewers were charged with identifying proposals that are ready for IND filing in not more than 4 years and were concerned that this plan was not sufficiently developed to achieve this.

The applicant highlights reviewer comments regarding the generation of dopaminergic neurons. Reviewers noted the applicants' clear demonstration to produce dopaminergic neurons but found insufficient details about how the scalability of this process would be achieved and the data presented did not show the rate of production of dopaminergic neurons of the A9 phenotype after sorting the cells. These were felt to be critical elements when considering the feasibility of developing a viable cell therapy. The applicant also notes that they have demonstrated behavioral improvement in one PD model and agree that additional models would be helpful. However, reviewers were concerned not simply by the use of additional models, but rather that adequate sensorimotor functional tests and tests for dyskinesias in the appropriate models were not considered or discussed. Additionally, the proposed long-term follow-up in the animal models

was not adequate to test for possible side effects such as the onset of dyskinesias. Reviewers also felt that issues of immunosuppression are an important consideration for any proposed cell therapy aimed at patients and deserved to be addressed in more detail in the application.

So although we do agree that this proposal has several strengths, there are also a number of important deficiencies that were appropriately considered and justify the recommendations made by the GWG reviewers.

This response provides an overall assessment by CIRM staff, based on our careful review of each of the points raised by the applicant. A point-by-point response would require reference to confidential or proprietary information. CIRM staff is prepared to provide that at the ICOC meeting, should a member so request.

The enclosed letter represents the views of its author(s). CIRM assumes no responsibility for its accuracy.

In addition, a copy of the CIRM Review Summary for this application is provided for reference.

Oct 22, 2007

To: Mr. Robert Klein, Chairman, Independent Citizens' Oversight Committee (ICOC)
Dr. Alan Trounson, President, CIRM

Re: DR1-01491: Develop a cell replacement therapy for Parkinson's disease using human embryonic stem cells

Dear Mr. Klein, Dr. Trounson and members of the ICOC:

We are writing to petition CIRM and the ICOC on behalf of our grant application "DR1-01491: Developing a cell replacement therapy for Parkinson's disease using human embryonic stem cells" under RFA 09-01.

Of the 11 applications recommended for funding by the reviewers, none of them is directed to Parkinson's disease (PD). We also note that only 3 out of 11 applications recommended for funding proposed to use human embryonic stem cells (hESCs), a priority of Proposition 71. PD sufferers have played a pivotal role in supporting stem cell research and volunteered for cell transplants in large numbers. It is one of the few diseases where positive data and clinical experience is available with human patients. It is therefore disappointing to see a lack of support for an IND for this devastating disease.

Our application proposed to develop a curative therapy for PD by using dopamine neurons produced from hESCs to replace the loss of A9 dopamine neurons in PD. We are confident that the plan will lead to an IND and a clinical trial in 4-5 years. Although this application scored below the cutoff line, the reviewers made many positive comments about the scientific merits of the application and highlighted the many strengths of the application. The reviewers concluded that the proposal has "a sound scientific rationale based on decades of tissue and cell transplantation work in this field". Some of the positives identified are:

1. They agreed our proposal builds on solid scientific work. They agreed that our proposal addresses an unmet medical need and has potential for great impact in treating PD.
2. The reviewers concurred that we had provided a solid demonstration of our ability to produce dopaminergic neurons in sufficient numbers using materials suitable for clinical uses.
3. The reviewers found that our proposal was well outlined and explained, the milestones and a timeline were clearly stated, and that we had described a clear governance structure.
4. The reviewers agreed that we had assembled a strong multidisciplinary team from both the industry and academic institutions with each institution having the necessary infrastructure and facilities to support their assigned projects.
5. They unequivocally stated that the PI and the Co-PIs have the expertise and track record to provide leadership for this project. They also praised the significant regulatory expertise in our team (Dr. Rao is the former Chairman of FDA gene/cell therapy advisory committee) and the inclusion of an experienced project manager to coordinate the activities.

Indeed the strength of our proposal and the essential validity of our plan were confirmed by the invitation to join with a European consortium of 12 nations with Sweden being the leader, to a joint effort on stem cell replacement therapy for PD. The consortium has received 16 M for clinical trials but does not have the same expertise as what we have developed for GMP manufacturing of dopaminergic neurons from hESCs. The leading scientist/clinician for this project from the Lund University has invited us to participate in a joint effort and to work with the Wallenburg Foundation in Sweden for a joint initiative.

In contrast, the criticisms raised by the reviewers are relatively minor and are either easily addressed or have already been addressed but data were not included due to the space limitations imposed by the application structure. The main criticisms and our responses are summarized below.

1. No evidence was presented about the rate of production of the right type of dopaminergic neurons after purification. Response: We have shown strong preliminary data on producing the right type of dopaminergic neurons prior to purification and could have easily provided more data should there be more space (the application limited preliminary data to 4 pages).
2. The lack of additional rodent models for more functional testing. Response: We have demonstrated behavioral improvement in one PD rodent model and agree that additional models would help. Indeed we have also proposed functional tests in the monkey model that mimic more precisely the human condition. This was cited as a strength of our proposal.
3. The panel was concerned that immunosuppression was insufficiently addressed. Response: Based on human trials with fetal cells, immune rejection seemed not to be a problem for PD. However we did propose to address the issue in both the rodent and monkey models in our proposal (See page 15 of the Application, Part A).

We believe that the reviewers' concerns while valid were weighted too heavily against the many strengths they recognized and the merits of this strong proposal. The weaknesses noted are technical in nature and can be easily addressed by the team.

We and our collaborators on this application would like to petition CIRM to consider creative ways to provide funding to maintain this strong team and to build on their extraordinary efforts over the past year. Our grant proposal was built on a staged program with clear go/no-go decision points. The technical issues raised by the reviewers will have been unambiguously addressed by the end of the two-year process. Providing staged conditional funding to address these criticisms may allow us to prove the validity of our approach and provide further evidence of the likelihood of success. By funding and adding this PD Disease Team to the portfolio, there will be a CIRM-directed pathway toward clinical trials for PD. CIRM can provide leadership for the entire PD community and help bring basic, translational and disease team to work collaboratively toward the clinic. Without some CIRM support it will be difficult for us to collaborate with the European Consortium.

In summary, the social urgency to direct CIRM funding to PD is compounded by the CIRM's ten year horizon under Prop. 71. By funding this PD application, CIRM can concentrate and leverage the combined expertise of the PD researchers brought together in the application to help bring basic and translational work to the clinic in the form of a cure to PD. A delay of even one year for PD funding would be detrimental to the team members and run counter to the

intentions of Prop. 71, which we note specifically mentioned PD as a target for stem cell research. Even 2 years of funding will be important to keep the momentum for solving the PD problem.

Sincerely,

Xianmin Zeng, PI

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North Bay CIRM Shared Research Laboratory for Stem Cells & Aging
Buck Institute for Age Research

Mahendra Rao, Co-PI

Mahendra Rao, M.D., Ph.D.
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Adjunct Professor, Buck Institute for Age Research

REVIEW REPORT FOR CIRM RFA 09-01: DISEASE TEAM AWARDS I

DR1-01491: Develop a cell replacement therapy for Parkinson's disease using human embryonic stem cells

Recommendation: Not recommended for funding
First Year Funds Requested: $4,082,782
Final Score:
Total CIRM Funds Requested: $16,995,173

Public Abstract (provided by applicant)
Parkinson's disease (PD) is a devastating movement disorder caused by the death of dopaminergic neurons (a type of nerve cells in the central nervous system) present in the midbrain. These neurons secrete dopamine (a signaling molecule) and are a critical component of the motor circuit that ensures movements are smooth and coordinated.

All current treatments attempt to overcome the loss of these neurons by either replacing the lost dopamine, or modulating other parts of the circuit to balance this loss or attempting to halt or delay the loss of dopaminergic neurons. Cell replacement therapy (that is, transplantation of dopaminergic neurons into the brain to replace lost cells and restore function) as proposed in this application attempts to use cells as small pumps of dopamine that will be secreted locally and in a regulated way, and will therefore avoid the complications of other modes of treatment. Indeed, cell therapy using tissue-derived cells have been shown to be successful in multiple transplant studies. Work in the field has been limited however, partially due to the limited availability of cells for transplantation.

We believe that human embryonic stem cells (hESCs) may offer a potentially unlimited source of the right kind of cell required for cell replacement therapy. Work in our laboratories and in others has allowed us to develop a process of directing hESC differentiation into dopaminergic neurons. Parallel efforts by clinicians have identified processes to implant the cells safely and to follow their behavior in humans in a safe non-invasive fashion. Equally important, useful animal models for testing cell therapy have been developed. We therefore believe that the time is right to mount a coordinated team effort such as the one we have proposed to approval from the FDA to treat PD using dopaminergic neurons obtained from hESCs.

For this proposal we have built a California team with both scientists and clinicians that have the potential to translate a promising idea (a cell therapy for PD) to an IND submission. Our goals include: 1) Identifying a clinically compliant hESC line capable of differentiating into midbrain dopaminergic neurons; 2) Developing protocols for generating and purifying dopaminergic neurons on a large scale; 3) Transferring the protocols to a Good Manufacture Practice (GMP) facility and making clinical grade lots; 4) Testing the quality of the cells in suitable PD animal models (rodents and large animal models); 5) Collecting the data to submit to the FDA for permission to conduct a clinical trial.

This application to treat a currently non-curable disease (PD) meets CIRM's primary goal for Disease Team Research Awards and we believe our efforts will help take cell-based therapy for PD to the clinic.

Statement of Benefit to California (provided by applicant)
Parkinson's disease affects more than a million patients United States with a large fraction being present in California. California, which is the home of the Parkinson's Institute and several Parkinson's related foundations and patient advocacy groups, has been at the forefront of this research and a large number of California based scientists supported by these foundations and CIRM have contributed to significant breakthroughs in this field.

We have assembled a California based team of scientists and clinicians that aim to develop a cell replacement therapy for this currently non-curable disorder. We believe that this proposal which will hire more than thirty employees in California includes the basic elements that are required for the translation of basic research to clinical research. We believe these experiments not only provide a blueprint for moving Parkinson's disease towards the clinic for people suffering with the disorder but also a

generalized blueprint for the development of stem cell therapy for multiple neurological disorders including motor neuron diseases and spinal cord injury. The tools and reagents that we develop will be made widely available to Californian researchers and we will select California-based companies for commercialization of such therapies. We hope that California-based physicians will be at the forefront of developing this promising avenue of research. We expect that the money expended on this research will benefit the Californian research community and the tools and reagents we develop will help accelerate the research of our colleagues in both California and worldwide.

Review Summary

The goal of this proposal is to develop clinical grade dopaminergic neurons from human embryonic stem cells (hESCs) for the treatment of patients with Parkinson's disease (PD). PD is a neurodegenerative disorder caused by the loss of midbrain dopaminergic neurons. Currently, there are no cures for PD although several symptomatic treatments are available. Since the early 1980's, transplantation of dopaminergic neurons into the brain to replace lost cells and restore function has been evaluated as a promising therapy for PD. Efforts with cell transplantation have stalled primarily because of three major challenges: variable efficacy, undesirable side effects, and a lack of a reliable source of human cells. hESCs, which can proliferate indefinitely in culture and differentiate into any somatic cell type, offer a promising potential cell source for transplantation. To achieve the goal of this proposal, the applicant plans to identify a clinically compliant hESC line capable of differentiating into midbrain dopaminergic neurons and to optimize scalable protocols for the generation and purification of Good Manufacturing Practice (GMP)-compliant dopaminergic neurons from these cells. The applicant will then evaluate these neurons for efficacy and safety in small and large animal models of PD, and will determine the requirement for immune suppression. Based on these studies, the applicant will then develop an Investigational New Drug (IND) application for submission to the Food and Drug Administration (FDA).

Overall, reviewers agreed that this proposal has a sound scientific rationale based on decades of tissue and cell transplantation work in this field. However, important gaps in the preliminary efficacy data and the research plan lowered the panel's expectation of an IND filing within the four-year timeframe. The application was not recommended for funding.

Reviewers agreed that a significant body of research and clinical data supports the applicant's rationale to replace the loss of midbrain dopaminergic neurons in PD. They commented that the application builds on several decades of transplantation work in both preclinical models and human subjects. While human trials have demonstrated proof of concept, they have highlighted two issues. First, that efficacy is variable among patients, and that side effects have emerged, notably dyskinesias. Because hESC-derived dopaminergic neurons may circumvent the side effects observed in the initial trials of cell replacement approaches, reviewers felt the use of hESCs was justified. The significance of the proposal was noted by reviewers, as the proposed therapeutic addresses an unmet medical need and has potential for great impact. PD is a common disease with no available disease modifying medical or surgical therapies. Current medical and surgical therapies are effective in the control of PD symptoms at least in the first few years after onset. However, their long-term efficacy diminishes as degeneration of dopaminergic cells progresses.

Reviewers evaluated two key aspects of the preliminary data, 1) the production of a more pure and expandable source of dopaminergic cells than has been used previously, and 2) the preliminary efficacy data, both of which address key bottlenecks in advancing a successful therapy. First, reviewers noted the applicants' solid demonstration of the ability to generate dopaminergic neurons by a four-step process using xenogeneic-free reagents. The process was described as scalable by the applicant, but insufficient details were presented in the application regarding how scalability would be achieved. The purity of hESC-derived dopaminergic neurons achieved after sorting was approximately 80% by TH immunohistochemistry. However, no evidence was presented about the rate of production of dopaminergic neurons of the A9 phenotype, which has been shown in the literature to be the appropriate dopaminergic cell for transplantation in PD. Reviewers also raised concerns about the preliminary efficacy data. Although the applicant demonstrates improvement in rotational behavior at 12 and 16 weeks post transplantation, a substantially later time point than with conventional tissue sources, reviewers noted the critical lack of sensorimotor testing for functional efficacy. This was judged to be an important omission in

the plan, since there is a well-established battery of sensorimotor tests that better reflect the human condition than rotational behavior in the rodent model of PD. Finally, reviewers commented that the plan should include an assessment of efficacy in the dyskinesia rodent model in addition to the standard 6-hydroxydopamine (6-OHDA) model of PD. This must be included to assess the development of severe dyskinesias, one of the most serious side effects of early neural tissue transplantation in humans.

The research and development plan was well explained, and outlined graphically in the application. Reviewers praised the inclusion of preclinical studies in a large animal model, which will be crucial before embarking on a clinical trial in PD patients. However, reviewers mentioned that the time allotted for large animal experiments may not be sufficient, as testing for efficacy and the development of side effects, such as onset of dyskinesias, will very likely take longer than planned. Reviewers commented that long-term follow-up in both the rodent and the large animal models is necessary to test for the long-term stability of the hESC-derived dopaminergic neurons, tumor formation and migration. They also felt that these large animal studies should occur earlier in the timeline and result in a go/no go decision point. The panel was concerned that immunosuppression was insufficiently addressed in the application. Finally, necessary improvements to the plan include those discussed in the preceding paragraph: optimization of differentiation protocols to produce A9 dopaminergic neurons, inclusion of sensorimotor testing, and the addition of studies in the dyskinesia rodent model.

From a regulatory perspective, reviewers judged the project plan to be practical, targeting key obstacles in a logical order. Manufacturing methods appeared sufficiently well established to enable GMP production. Cell selection methods in development are currently used in clinical-scale manufacturing of cell therapy products, and reagent issues have been or are being addressed. Proposed milestones and a timeline were clearly stated. For the most part timelines seemed realistic, with the notable exceptions of the large animal studies and the time available for development of the GMP/clinical manufacturing methods. Clear go/no-go decision criteria at milestones were lacking.

Reviewers found that the principle investigator (PI) and the two Co-PIs have the necessary expertise and track record to provide leadership for this project. One reviewer, however, was concerned about the PI's lack of expertise in directing a clinically oriented project such as this one. On the other hand, another reviewer praised the PI's 45% time commitment to the project. The significant regulatory expertise present in the team members was viewed as a strength, as were the clear governance structure and the enlistment of an experienced project manager to coordinate the activities of the different researchers and institutions.

This is a multidisciplinary collaborative project from several industry and academic institutions. Reviewers agreed that each institution has the necessary infrastructure and facilities to support their assigned projects. The resources and budget were found to be adequate to complete the proposed project.

Overall, reviewers agreed that this proposal addresses an important unmet medical need and could potentially have a significant impact. However, they were not convinced that sufficient convincing preliminary data was presented in the application to justify moving forward with this award. As a result, the panel did not believe the proposal would result in an IND filing within the four-year timeframe.

The following scientific Grants Working Group members had a conflict of interest with this application:
None.